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EFFECT OF DOPAMINE SYSTEM ACTIVATION ON SUBSTANTIA NIGRA PARS RETICULATA OUTPUT NEURONS: VARIABLE SINGLE-UNIT RESPONSES IN NORMAL RATS AND INHIBITION IN 6-HYDROXYDOPAMINE-LESIONED RATS[1]

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Abstract

Previous single-unit recording studies have revealed that randomly selected pars reticulata neurons respond in a higly variable and complex fashion to intravenous administration of the dopamine agonist, apomorphine. The current studies were undertaken (*1*) to assess whether the variable pattern of responses of reticulata neurons to intravenous apomorphine correlates with their sites of projection and (*2*) to determine how reticulata responses to apomorphine might be altered by the presence of striatal dopaminergic supersensitivity.

Extracellular, single-unit recording studies were conducted in anesthetized, paralyzed rats. Pars reticulata neurons were identified by antidromic activation from either the ventromedial nucleus of the thalamus or superior colliculus. Neurons of both subpopulations exhibited similar, highly variable changes in firing rate during the 10-min period immediately following intravenous injection of 320 μg/kg of apomorphine, a dose of the drug considered sufficient to stimulate striatal postsynaptic dopamine receptors. These responses, which were not qualitatively different from those previously observed among reticulata cells not distinguished on the basis of projection site, could be reversed by subsequent administration of dopamine antagonist drugs. In contrast to the variable responses in normal animals, the same dose of apomorphine caused a rapid and usually total inhibition of pars reticulata cell firing in rats which received 6-hydroxydopamine lesions of the nigrostriatal dopamine pathway 6 to 8 weeks prior to recording experiments. These inhibitions of firing could also be reversed by administration of dopamine antagonists. The results demonstrate that the variable responses of pars reticulata neurons to intravenous apomorphine are not dependent on projection site and, therefore, suggest that dopamine system activation typically results in transmission of complex, nonuniform messages to several, and perhaps all, reticulata output sites. However, the presence of striatal dopaminergic supersensitivity appears to exaggerate inhibitory, dopamine-mediated influences upon pars reticulata output neurons selectively and consistently.

The substantia nigra pars reticulata has, in recent years, gained recognition as an important relay station in the extrapyramidal control of movement. Since this area both receives a prominent input from the striatum and sends projections to several premotor nuclei (Graybiel and Ragsdale, 1979), it constitutes a critical link in the transmission of striatal commands to motor output centers. Understandably, much attention is being directed toward resolving the question of how striatal dopamine system activation affects function of nondopaminergic pars reticulata output neurons, as well as the several nuclei which, in turn, receive inputs from the pars reticulata. Numerous behavioral studies have made significant progress toward delineating details about which reticulata projections mediate specific dopamine agonist-induced behaviors and movements (Dichiara et al., 1977, 1978; Scheel-Krüger et al., 1977; Olianas et al., 1978; Redgrave et al., 1980; Kilpatrick et al., 1982; Childs and Gale, 1983; Cools et al., 1983). For instance, some investigations have suggested that nigral output pathways to the superior colliculus, dorsal reticular formation, and mesencephalic tegmentum control postural symmetry and mediate dopamine-related stereotypies, while nigral projections to the ventromedial nucleus of the thalamus appear to regulate gross motor function or the level of locomotor activity (Scheel-Krüger, 1982).

Recent single-unit recording studies in this laboratory have shown that intravenous administration of the dopamine agonist, apomorphine, elicits highly variable changes in the firing rates of randomly selected neurons of the substantia nigra pars reticulata (Waszczak et al., 1984). Cells exhibited increases, decreases, or no changes in firing after administration of a 320 μg/kg dose of the drug. This variable pattern of responses was observed in both chloral hydrate-anesthetized rats as well as

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conscious, paralyzed rats given this dose of apomorphine. These results lead to the tentative conclusion that striatal dopamine receptor activation does not result in transmission of a uniform message to all pars reticulata neurons. Extending this line of thinking, the possibility exists that subpopulations of reticulata neurons which project to different premotor nuclei may receive qualitatively different messages from the striatum, thereby directing them to carry out different movement-related functions. Although the likelihood of this arrangement may be limited by the fact that some reticulata neurons have branching axons which project to two or more of these nuclei (Deniau et al., 1978; Beckstead and Frankfurter, 1982), it seems plausible that functional differences might still exist between populations of reticulata neurons with different termination sites. Thus, one of the goals of the present study was to determine whether pars reticulata neurons which project to either of two major but behaviorally distinct output nuclei, the superior colliculus and ventromedial thalamus, respond in different but more internally consistent ways to intravenous apomorphine. If so, the variable responses to apomorphine which were observed in the previous study might be attributable to the selection of reticulata neurons from subpopulations which respond differently to dopamine system stimulation.

A second objective of the current study was to learn more about the nature of the striatal, dopamine-mediated influence upon the pars reticulata by exaggerating the strength of this influence. To accomplish this, effects of apomorphine were monitored in animals with striata conferred supersensitive to dopamine by previous 6-hydroxydopamine lesions of the ascending dopaminergic projection.

Materials and Methods

Single-unit recording techniques. Studies were conducted in gallamine-paralyzed, artificially respired, locally anesthetized, male Sprague-Dawley rats (250 to 400 gm). This procedure was adopted here because previous single-unit recording studies have shown that anesthesia affects the response of another striatal output nuclei, the globus pallidus, to apomorphine (Bergstrom et al., 1984). In addition, 2-deoxyglucose studies have indicated that anesthesia affects the response of the substantia nigra to apomorphine (Grome and McCulloch, 1981). All procedures were carried out in strict compliance with rules set forth in the National Institutes of Health's *Guide for the Care and Use of Laboratory Animals* (Cohen et al., 1974). During all preparative surgical procedures, animals were anesthetized with the short-acting anesthetic, halothane (Ayerst Laboratories Inc., New York, NY). All incision sites and pressure points were thoroughly infiltrated with the long-acting local anesthetic mepivacaine hydrochloride (Breon Laboratories Inc., New York, NY). Eye drops of tetrahydrozoline hydrochloride (Pfizer Inc., New York, NY) solution were applied intermittently to prevent corneal drying. After completion of surgical preparations, rats were paralyzed with gallamine triethiodide (Davis-Geck, New York, NY), 16 mg/kg, given through a tail vein. Halothane administration was discontinued, and animals were respired on room air at a rate adjusted to maintain an expired CO_2 level of 3.5 to 4.2% as measured by a CO_2 analyzer. Body temperature was maintained at 36 to 38°C.

The extracellular, single-unit activity of substantia nigra pars reticulata neurons was monitored using standard electrophysiological techniques (Bunney et al., 1973; Waszczak et al., 1980). Single-barrel glass electrodes were filled with a solution of 1% Pontamine Sky Blue (Gurr, High Wycombe, Bucks, England) in 2 M NaCl. Their resistances ranged between 3.5 and 6.0 megohms, measured at 135 Hz. Electrodes were passed through a small burr hole in the skull and then lowered to the level of the substantia nigra with a hydraulic microdrive. Techniques for amplifying, discriminating, and counting extracellular action potentials have been described in detail elsewhere (Bunney et al., 1973; Waszczak et al., 1980).

All pars reticulata neurons included in these studies were selected on the basis of their ability to be activated antidromically from either the ipsilateral ventromedial nucleus of the thalamus or the superior colliculus. For thalamic stimulation, a bipolar, concentric stimulating electrode (NE-100, David Kopf Instruments) was stereotaxically positioned in the left ventromedial thalamus: 1.1 mm lateral, 4620 μm anterior, −1 mm ventral, according to the atlas of König and Klippel (1970). For stimulation of the superior colliculus, a 2 × 2 array of four electrodes (approximately 1-mm tip separation; insulated to within 0.5 mm of tips) was positioned within the deep layers of the left superior colliculus: 0.7 and 1.7 mm lateral, 620 to 1610 μm anterior, 0.5 to 1.0 mm ventral, according to the atlas of König and Klippel (1970). Stimuli were applied to three electrodes and returned through the fourth.

Stimulation consisted of square pulses, 0.2 msec in duration and 0.1 to 0.4 mA in intensity. The following criteria were used to assess whether pars reticulata neurons could be activated from one of these projection sites: (*1*) constant latency of the evoked response, (*2*) an ability of the neurons to follow high frequency (>300 Hz) stimulation, and (*3*) demonstration of collision between spontaneous and antidromically evoked spikes.

After ascertaining that a pars reticulata neuron could be antidromically excited from the thalamus or superior colliculus, a 5-min period of its base line activity was recorded. After the base line period, a single intravenous injection of apomorphine (Merck Chemical Div., Rahway, NJ), 320 μg/kg; (1 μmol/kg), was administered through a tail vein. Neuronal firing was monitored for at least 10 min after drug injection. The percentage of change in cell firing was determined for each minute of this 10-min period by comparing average firing rates from successive 10-sec intervals after apomorphine administration with the average base line firing rate before drug. Only one cell was monitored per rat.

Identification of cells. All neurons were located within the substantia nigra pars reticulata within the following stereotaxic coordinates, according to the atlas of König and Klippel (1970): 1760 to 2580 μm anterior, 1.7 to 2.5 mm lateral, and −1.5 to −2.5 mm ventral. The electrophysiological characteristics of these cells have been fully described elswhere (Guyenet and Aghajanian, 1978; Waszczak et al., 1980). These characteristics, as well as their location just ventral to the easily recognizable neurons of the substantia nigra pars compacta (Bunney et al., 1973; Guyenet and Aghajanian, 1978; Waszczak et al., 1980), made possible tentative identification of pars reticulata neurons during the recording period. Antidromic activation of neurons from one of the known reticulata projection sites aided in their confirmation. Later verification of the exact recording site was accomplished by passing a 15-μA current through the electrode at the end of the experiment. This caused a small amount of the Pontamine Blue dye to be deposited at the electrode tip. Animals were then decapitated, and their brains were removed, fixed, sectioned, mounted, and stained. The location of the blue spot identified the recording site.

6-Hydroxydopamine lesion technique. Animals were anesthetized with chloral hydrate (Sigma Chemical Co., St. Louis, MO), 400 mg/kg, i.p., and mounted in a stereotaxic apparatus. Unilateral 6-hydroxydopamine (Sigma Chemical Co.) lesions were placed in the left nigrostriatal pathway at a site just anterior to the substantia nigra, corresponding to section A 3180 μm of König and Klippel (1970). An injection cannula was positioned 1.1 mm lateral to the midline suture and lowered to a point just above the ascendng dopaminergic bundle (−2.9 mm according to König and Klippel (1970)). 6-Hydroxydopamine (6 μg/3 μl of 0.1% ascorbic acid in 0.9% NaCl) was injected slowly over a period of 2 min. The cannula was allowed to remain in place for an additional minute, and it was then removed slowly. Animals recovered from the anesthesia within 1 to 1½ hr after the completion of the lesioning procedure.

All electrophysiological studies were conducted 6 to 8 weeks after animals received 6-hydroxydopamine lesions. At the end of recording experiments, animals were decapitated, and their brains were rapidly removed. Striata from both the lesioned and unlesioned sides were dissected and quickly frozen to −70°C. The posterior portion of the brains was fixed in buffered formalin phosphate solution (Fisher Scientific Co., Fairlawn, NJ) for later histological verification of the recording site and examination of the cannula track and lesion site. The dissected striata were processed for analysis of dopamine levels by high pressure liquid chromatography with electrochemical detection. Whole striata were sonicated in 0.2 N perchloric acid and centrifuged, then the supernatant was analyzed directly according to the technique of Wagner et al. (1982). The tissue extract was passed over a Waters C_{18} μBondapak column with a sodium phosphate mobile phase, pH 4.5, with 2% acetonitrile at a flow rate of 1.2 ml/min. Dopamine levels in the striata on the lesioned side averaged less than 5% of those on the unlesioned side. Rats were excluded from the study if the striatal dopamine content of the lesioned side was greater than 10% of that on the unlesioned side.

Results

Responses of nigrothalamic and nigrotectal neurons to intravenous apomorphine (1 μmol/kg). Substantia nigra pars reticulata neurons were identified as either nigrothalamic or nigrotectal neurons by antidromic activation from the ventromedial nucleus of the thalamus or the superior colliculus, respectively. Pars reticulata neurons projecting to these two sites responded to intravenous administration of apomorphine (320 μg/kg; 1 μmol/kg) in a qualitatively similar fashion. Cells of both populations exhibited highly variable changes in firing rate during the 10-min period immediately following drug injection. Significant numbers of neurons markedly increased their firing rates, many cells were inhibited, some showed little or no change in firing rate, and others showed multiphasic or rapidly fluctuating changes in firing rate (Figs. 1 and 3). Of 22 neurons which were identified as nigrothalamic cells, 7 (32%) exhibited increases in firing by more than 25% of their base line rates, 7 (32%) were inhibited by more than 25%, and the remaining 8 cells (36%) were relatively unaffected (±25% changes in firing) 5 to 10 min after apomorphine injection. Firing changes ranged from total inhibition to an average increase in firing by 119%. The average change in rate for all nigrothalamic cells tested was an increase in firing by 15 ± 19% ($n = 22$).

The pattern of responses of nigrotectal neurons to the same intravenous dose of apomorphine was also highly variable (Figs. 1 and 3). Most cells showed either increases in firing or no sustained changes in rate. Several cells exhibited dramatic, multiphasic fluctuations in firing. There tended to be somewhat fewer instances of marked and sustained inhibitions of firing than were observed in the population of nigrothalamic neurons described above. Of 22 neurons which were antidromically activated from the superior colliculus, 8 cells (36%) exhibited increases in firing by 25% or more, only 3 cells (14%) were inhibited by 25% or more, and the remaining 11 cells (50%) showed no changes in firing (± 25%) during the period 5 to 10 min after apomorphine injection. Firing changes ranged from an inhibition by 42% to an excitation by 140%. The average response of all nigrotectal neurons monitored was an increase in firing by 16 ± 9% ($n = 22$).

Subsequent intravenous administration of dopamine antagonists, haloperidol or spiroperidol, reversed the effects of apomorphine on the activity of both nigrothalamic and nigrotectal neurons (Fig. 1). The apomorphine-induced excitation of five of six nigrotectal neurons and the responses of the three cells which exhibited decreases in rate were reversed by a 0.2 mg/kg intravenous dose of haloperidol. Similiarly, five of six nigrothalamic neurons which were stimulated by apomorphine and each of the seven cells which were inhibited by apomorphine could be restored to their base line firing rates by intravenous administration of halperidol (0.2 mg/kg) or spiroperidol (0.2 to 0.4 mg/kg).

Responses of nigrothalamic and nigrotectal neurons to intravenous apomorphine (1 μmol/kg) in rats with nigrostriatal lesions. In contrast to the highly variable responses observed in normal rats, apomorphine (1 μmol/kg) caused a more consistent and often total inhibition of firing of both nigrothalamic and nigrotectal neurons in rats which had received 6-hydroxydopamine lesions of the nigrostriatal dopaminergic pathway 6 to 8 weeks earlier. The inhibition of cell firing was typically

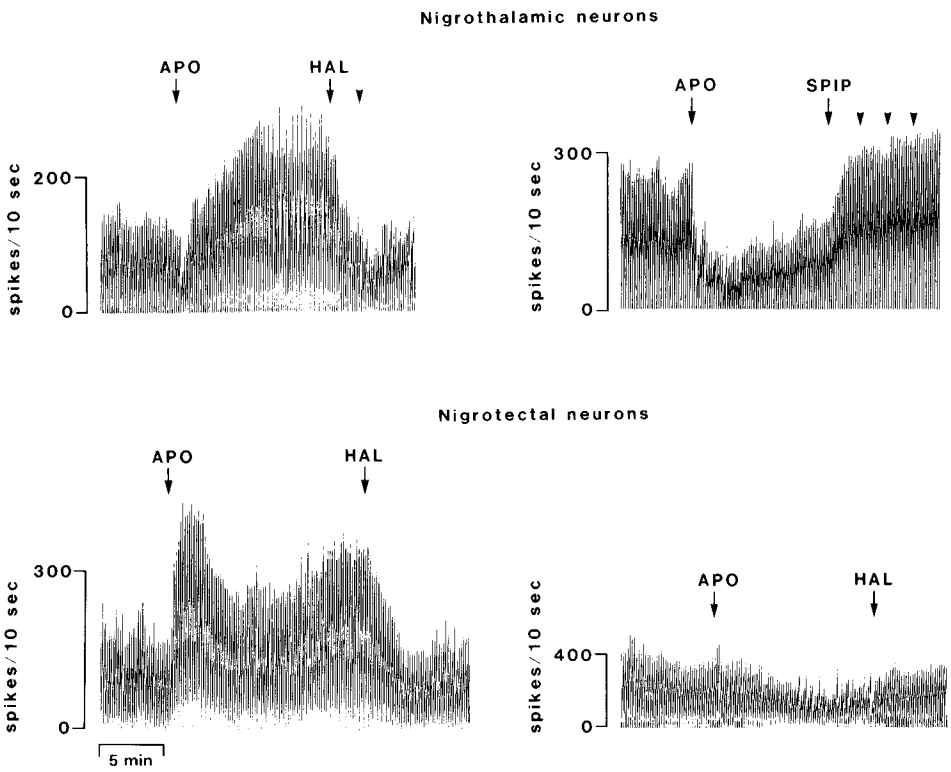

Figure 1. Effects of intravenous administration of apomorphine (*APO*; 1 μmol/kg) on single-unit activity of substantia nigra pars reticulata neurons which were identified on the basis of projection site. *Top*, Examples of apomorphine-induced increases and decreases in the firing of reticulata neurons antidromically activated from the ipsilateral ventromedial thalamus. *Bottom*, Examples of apomorphine-induced changes in firing of reticulata neurons antidromically activated from the ipsilateral superior colliculus. Note that subsequent intravenous administration of the dopamine antagonists, haloperidol (*HAL*; 0.2 mg/kg) or spiroperidol (*SPIP*; 0.2 mg/kg), reversed both the increases and decreases in firing elicited by apomorphine. Additional injections of antagonist produced little further effect.

apparent within the first 3 min after apomorphine administration and was nearly maximal by 5 min after injection. In a few cases, cell firing rebounded to above the base line rate during the 5 to 10 min period after the drug, but, more commonly, firing remained markedly depressed or totally inhibited (Figs. 2 and 3).

Of 17 nigrothalamic neurons tested in 6-hydroxydopamine-lesioned rats, 14 (82%) were inhibited by more than 25% of their base line firing rates 5 to 10 min after apomorphine injection. In fact, for most of these cells (10 of the 14), firing was totally inhibited, although it was still possible to elicit spikes by stimulation of the ventromedial thalamus. For this group of 14 nigrothalamic neurons, the average change in firing 5 to 10 min after apomorphine was an inhibition by 93 ± 5%. Of the remaining nigrothalamic cells recorded in lesioned rats, two cells (12%) exhibited increases in firing by more than 25%, and one cell (6%) was unaffected (± 25%) by the drug.

A similar set of responses to intravenous apomorphine was observed for nigrotectal neurons recorded in 6-hydroxydopamine-lesioned rats. Of 21 neurons activated from the superior colliculus, 17 (82%) exhibited inhibitions of firing by 25% or more. Again, most of these cells (11 of the 17) were totally or nearly totally inhibited, although spikes could still be evoked antidromically. The average change in firing 5 to 10 min after drug injection for this group of 17 neurons was an inhibition by 82 ± 6%. Two (9.5%) of the remaining nigrotectal neurons were excited by more than 25%, and two cells (9.5%) were unaffected (± 25%) by apomorphine administration.

Administration of haloperidol or spiroperidol, sometimes in combination with *cis*-flupenthixol, reversed the inhibitory effects of apomorphine on nigrotectal and nigrothalamic neurons recorded in 6-hydroxydopamine-lesioned rats (Fig. 2). This typically required higher doses of antagonists than were necessary to reverse the increases and decreases in reticulata cell activity observed in the unlesioned rats. Doses of haloperidol ranging from 0.2 mg/kg to 1.0 mg/kg (average 0.54 mg/kg, n = 18) or doses of spiroperidol ranging from 0.4 to 2.0 mg/kg (average 1.0 mg/kg, n = 8) were required to reverse the inhibition of firing elicited by apomorphine. In five cases, when 0.8 mg/kg of haloperidol or 1.2 to 2.0 mg/kg of spiroperidol were unable to reverse the effect of apomorphine, *cis*-flupenthixol (0.2 to 0.8 mg/kg) was then administered. This typically resulted in a reversal of the inhibition and raised the possibility that the latter antagonist was more effective than haloperidol or spiroperidol in blocking the actions of apomorphine in this situation. However, in other instances when *cis*-flupenthixol was administered first, the effects of apomorphine could not be reversed, and additional injections of haloperidol or spiroperidol were required.

Discussion

The substantia nigra pars reticulata and the internal segment of the globus pallidus occupy a critical position in the extrapyramidal motor system because these areas serve as the only output nuclei of the basal ganglia (Nauta and Mehler, 1966; Graybiel and Ragsdale, 1979). The current surge of interest directed at understanding these output centers, and especially the substantia nigra pars reticulata, stems from at least two perspectives. First, the activity of the pars reticulata has been considered a reflection of striatal function since this area receives a massive, direct striatal outflow. So, in a sense, the pars reticulata may provide a window for viewing striatal processing. Second, the pars reticulata itself can be regarded as a key processing area since it gathers and then disseminates striatal commands to the appropriate motor effector nuclei outside the basal ganglia.

The intent of the current studies has been to gather information pertinent to both of the above perspectives. First, it was hoped that studying the effects of intravenous apomorphine administration on the activity of substantia nigra pars reticulata neurons would provide some insight into how the striatum, and particularly the nigrostriatal dopamine system, normally exerts its influence upon movement-generating systems originating in the pars reticulata. In addition, attempts were made to evaluate how two subpopulations of reticulata neurons, distinguished on the basis of their projections to behaviorally distinct premotor nuclei, would respond to apomorphine administration. If different response patterns could be correlated with different reticulata projection sites, then our understanding of the role of the pars reticulata as an information-processing and distribution site would be extended considerably. Finally, it was of special interest to determine how the existence of striatal dopaminergic supersensitivity might disrupt the normal responses of reticulata neurons to dopamine system stimulation.

Results of these and previous studies (Waszczak et al., 1984) have yielded interesting answers to some of these questions and raised others. The responses of pars reticulata neurons to an intravenous dose of apomorphine, considered sufficient to stimulate striatal postsynaptic dopamine receptors, have been highly variable and complex. Our earlier studies (Waszczak et al., 1984) confirmed that a significant degree of this variability seems to arise from the striatum since striatal kainic acid lesions could reduce, but not totally abolish, the variable reticulata responses to this dose of apomorphine. Thus, the existence of this complexity implies that striatonigral transmission is typically not homogeneous. This nonuniformity may provide an important means for directing motor effector nuclei to carry out complex or intermittent behaviors.

The current findings extend those of our previous study in that they also reveal that this variability does not correlate with the site to which reticulata neurons project. Populations of both nigrothalamic and nigrotectal neurons exhibited similar and equally variable responses to the same 320 μg/kg dose of the drug. The increases and decreases in activity of both nigrothalamic and nigrotectal neurons were reversed by dopamine antagonist administration. The nonuniform pattern of responses to apomorphine observed among these two subpopulations of neurons did not differ appreciably from those previously reported for randomly selected pars reticulata neurons which were not identified by projection site (Waszczak et al., 1984). In all cases, significant numbers of cells exhibited increases, decreases, no changes, or minute-to-minute fluctuations in firing after intravenous administration of the drug. Thus, dopamine system activation appears to result in transmission of complex and nonuniform messages to several, and perhaps all, pars reticulata projection sites. Exactly how this complexity translates into discrete motor output remains to be clarified.

In marked contrast to the variable responses seen in normal rats, apomorphine elicited much more consistent changes in reticulata cell firing in animals which had received lesions of the nigrostriatal dopamine neurons 6 to 8 weeks earlier. In these lesioned rats, almost all cells from both nigrothalamic and nigrotectal populations exhibited rapid and often total inhibitions of firing after administration of 320 μg/kg of apomorphine. Similar inhibitory responses were almost never observed in unlesioned animals. This pronounced change in the pattern of reticulata responses in animals with striatal lesions is interesting for several reasons. First, the presumed presence of striatal dopaminergic supersensitivity in these animals did not simply exaggerate the widely variable changes in reticulata cell firing which were typically elicited by apomorphine. There was no indication that excitatory as well as inhibitory responses were potentiated, although in unlesioned rats approximately one-third of reticulata neurons normally displayed increases in firing. Rather than a quantitative shift in the magnitude of all types of reticulata responses, the presence of dopaminergic

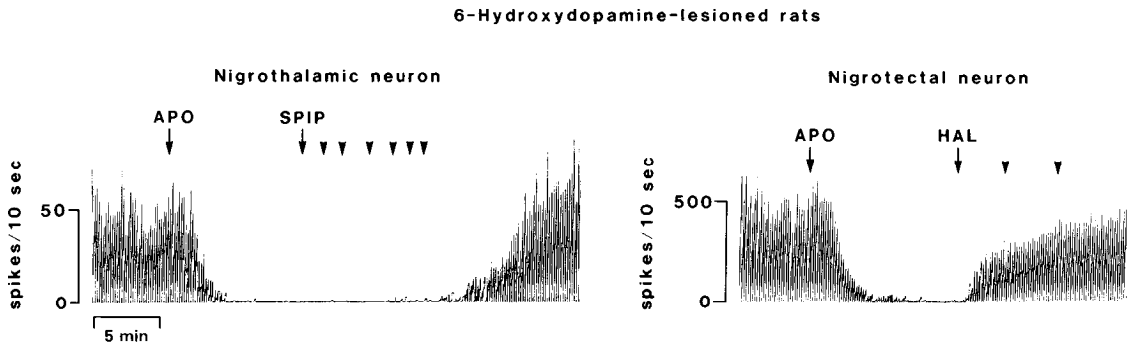

Figure 2. Effects of intravenous administration of apomorphine (*APO*; 1 μmol/kg) on single-unit activity of nigrothalamic (left) and nigrotectal (*right*) neurons recorded in animals which received 6-hydroxydopamine lesions of the nigrostriatal dopamine neurons 6 to 8 weeks prior to the recording experiment. Firing of both neurons was almost totally inhibited 3 to 5 min after apomorphine administration. Spiroperidol (*SPIP*; cumulative dose, 1 mg/kg) and haloperidol (*HAL*; cumulative dose 0.6 mg/kg) reversed the apomorphine-induced inhibitions of firing.

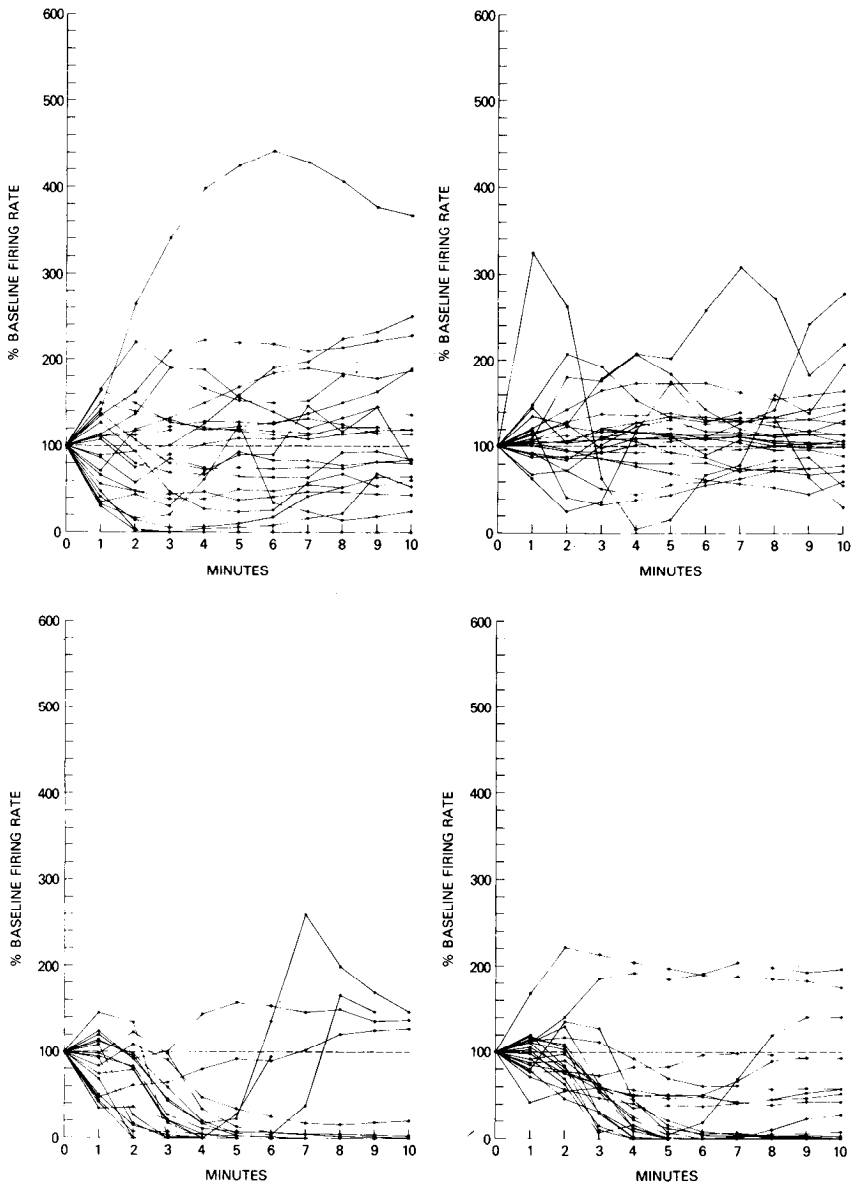

Figure 3. Minute-to-minute changes in firing of individual substantia nigra pars reticulata neurons from 1 to 10 min after intravenous injection of apomorphine (1 μmol/kg). Rates are expressed as a percentage of the base line firing rate during the 5-min period before drug injection. *Top*, Effects of apomorphine on nigrothalamic neurons (*left*) and nigrotectal neurons (*right*) recorded in normal animals. *Bottom*, Effects of apomorphine on nigrothalamic neurons (*left*) and nigrotectal neurons (*right*) recorded 6 to 8 weeks after rats received ipsilateral 6-hydroxydopamine lesions of the nigrostriatal dopamine neurons.

supersensitivity seemed to induce a qualitative change in the nature of the response evoked by dopamine system stimulation. While this qualitative change probably reflects a denervation-induced alteration in some aspects of striatal processing and output function, it is not possible to ascertain from these studies precisely what the change might be. One likely explanation is that striatal dopaminergic supersensitivity somewhat selectively exaggerates inhibitory, dopamine-mediated influences upon the pars reticulata, whereas in normal, nonsupersensitive animals, these inhibitory striatal influences may be moderated by, or in balance with, striatal or nonstriatal excitatory influences. Relevant to this point are the direct excitatory effects of dopamine upon pars reticulata neurons when it is applied by microiontophoresis (Ruffieux and Schultz, 1980; Waszczak and Walters, 1983a). In addition, applied dopamine reduces the inhibitory responses of these cells to applied GABA (Waszczak and Walters, 1983a) as well as GABA released physiologically (Waszczak and Walters, 1983b). The ability of dopamine to excite these cells directly or to modulate their responses to GABA raises the possibility that systemically administered apomorphine might also exert some direct, nonstriatal excitatory effects upon reticulata cell firing. However, while in normal rats the net effect of dopamine system stimulation may be a reflection of a dynamic balance between several opposing influences, in supersensitive rats the inhibitory influences upon these neurons appear to predominate, overshadowing the direct excitatory effects.

Although an exaggeration of inhibitory influences can account for the different responses of lesioned and unlesioned rats to an identical 320 μg/kg intravenous dose of apomorphine, it does not address the issue of whether the nature of the response elicited is simply a function of the degree of dopamine receptor sensitivity and the drug dose. For instance, it is not clear whether much lower doses of apomorphine might cause variable changes in cell firing in lesioned, supersensitive rats. However, we have determined that higher intravenous doses of apomorphine (1 mg/kg) do not produce in normal rats electrophysiological responses similar to those observed in the supersensitive animals. The responses observed were similar with respect to variablility to those observed after the 320 μg/kg dose of apomorphine (J. R. Walters and B. L. Waszczak, unpublished observations). Thus, whatever the underlying neuronal mechanism, striatal dopaminergic supersensitivity appears to induce a qualitative, rather than simply quantitative, change in the nature of the responses of reticulata output pathways to postsynaptic dopamine receptor stimulation.

Finally, these results may have important implications with respect to the neuropathology and treatment of Parkinson's disease. Our results suggest that in Parkinsonian brain, as in rats with long-standing lesions of the nigrostriatal dopamine pathway, there may exist critical changes in the responsiveness of basal ganglia output sites, such as the pars reticulata, to dopamine receptor stimulation. The gradual development of striatal dopaminergic supersensitivity during the course of the disease could lead to a qualitative change in the nature of movement-related messages communicated to motor effector sites upon stimulation of supersensitive dopamine receptors. The emergence of this qualitative change in reticulata output function may ultimately confound attempts to restore Parkinsonian patients to "normal" functioning by treatment with dopaminergic drugs. In fact, it is conceivable that a developing tendency for dopamine receptor stimulation to silence reticulata output function may contribute to the "on-off" phenomenon characteristic of late-stage Parkinson's disease.

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